CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Deputy Office Director Decisional Memo

Date	October 21, 2011
From	Ellis F. Unger, M.D., Deputy Director, ODE-I
Subject	Deputy Office Director Decisional Memo
NDA#	202067
Applicant Name	Lundbeck Inc.
Date of Submission	December 23, 2010
PDUFA Goal Date	October 23, 2011
Proprietary Name / Established (USAN) Name	Onfi clobazam
Dosage Forms / Strength	Oral tablets: 5 mg, 10 mg, and 20 mg
Indication	… adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients 2 years of age or older
Action:	*Approval*

Material Reviewed/Consulted Action Package, including:	
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Medical Officer Clinical Review Efficacy/Safety	Philip Sheridan/ Gerard Boehm, Sally Yasuda
Clinical Pharmacology Review	Seongeun Julia Cho, Ta-Chen Wu, Angela Men
Pharmacometrics	Joo-Yeon Lee, Yaning Wang
Pharmacogenomics	Hobart Rogers, Michael Pacanowski
Statistical Review	Ohidul Siddiqui, Kun Jin, Jim Hung
Pharmacology Toxicology	Edward Fisher, Lois M. Freed, Adele Seifried, David Jacobson Kram, Abby Jacobs, Paul Brown, William Taylor
Chemistry Manufacturing and Controls	Akm Khairuzzaman, Martha Heimann, Ramesh Sood, Angelica Dorantes, Patrick Marroum, Teshara Bouie, Don Henry
QT Interdisciplinary Review Team	Joanne Zhang
Statistical Review - Carcinogenicity Study	Min Min, Karl Lin
Controlled Substance Staff	Alicja Lerner, James Hunter, Corinne Moody, Michael Klein
Environmental Assessment	Akm Khairuzzaman
Division of Scientific Investigations	Antoine El-Hage, Yolanda Patague, Tejashri Purohit-Sheth, Susan Thompson, Jean Mulinde, Leslie Ball
Division of Medication Error Prevention and Analysis, Office of Surveillance and Epidemiology	Lubna Merchant, Laurie Kelly, Kelley Simms, Cindy Kortepeter, Ann McMahon, Carol Holquist
Division of Risk Management, Office of Surveillance and Epidemiology	Twanda Scales, Melissa Hulett, LaShawn Griffiths
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Cross-Discipline Team Leader	Norman Hershkowitz
SEALD Labeling Team	Jun Yan, Eric Brodsky, Ann Marie Trenatacosti
Director, Division of Neurology Products	Russell Katz

Reference ID: 3033073

Action:

The Division of Neurology Products is recommending approval of clobazam, 5-, 10-, and 20-mg Tablets for oral administration for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients 2 years of age or older. I concur with their recommendation for approval.

Description:

Clobazam is a small molecule oral 1,5 benzodiazepine with anticonvulsant, sedative, anxiolytic, and muscle relaxant properties.

Disease Background:

LGS is a severe, difficult-to-treat form of child-onset epilepsy, characterized by frequent seizures of multiple types, as well as abnormal development, psychological, and behavioral problems. Onset is generally between the ages of 3 and 8, and the disease can persist into reproductive age and beyond. Multiple daily seizures are typical; the most troublesome of these are drop attacks. Drop attacks may occur in relation to tonic, atonic, or myoclonic seizures, and may result in significant injury. (Many patients with LGS regularly wear helmets and face guards to prevent injury.) Because drop attacks are the most clinically significant manifestation of LGS, clinical trials for assessment of treatments for LGS generally assess drop attacks as the primary outcome measure.

LGS is estimated to represent approximately 1 to 2% of all childhood epilepsy. Its prevalence in the U.S. is estimated to be fewer than 200,000 people, and, in accordance with 21 CFR 316.20, clobazam was designated an orphan drug for LGS in December, 2007.

Regulatory History:

Clobazam is not approved in the U.S. for any indications; however, it has been marketed (as Frisium; Urbanol) in numerous countries for some 4 decades, where it is used for the treatment of anxiety and epilepsy.

Clinical development of clobazam for treatment of seizures associated with LGS was conducted under IND 70125, submitted in May, 2005 by Ovation Pharmaceuticals, Inc. (now Lundbeck Inc.). Clobazam's original nonclinical studies were conducted prior to 1978, the year when Good Laboratory Practice (GLP) for conducting nonclinical laboratory studies was promulgated by FDA. In a pre-IND meeting in October, 2004, the Division apprised the sponsor of additional specific nonclinical studies that would be needed to support clinical development of clobazam for treatment of LGS.

During an end-of-phase 2 meeting in May, 2007, the Division expressed concern regarding the potential for development of tolerance, with diminishing long-term efficacy. To address this concern, the maintenance phase for the pivotal phase 3 study was lengthened from 8 to 12 weeks at the suggestion of the Division.

Chemistry Manufacturing and Controls (CMC):

The application was deemed acceptable for approval from a CMC perspective, and there are no pending issues.

Pharmacology/Toxicology:

Dr. Fisher noted that the general nonclinical studies, conducted prior to 1978, do not meet GLP standards, and outlined a number of deficiencies.

- Signed pathology reports: generally not provided for these studies.
- Chronic oral toxicity studies in rat: incomplete microscopic examination; individual line listings and summary histopathology tables not provided. No toxicokinetic analyses.
- Chronic oral toxicity studies in dog: individual line listings not provided; evidence of toxicity secondary to parasites.
- Chronic oral toxicity study in monkey: histopathology conducted only on animals that died prematurely; evidence of compromised general health (i.e., malaria, tuberculosis, mites).
- Dietary carcinogenicity studies in mouse and rat: early deaths, fighting-induced injuries; inability to ensure accurate dosing (animals were housed together in groups); no documentation of stability of drug in diet; no toxicokinetic analysis; no documentation that a full battery of tissues was examined microscopically; no signed study report.
- Reproductive and developmental studies: lack of evidence of toxicity in the F_0 generation; inadequate justification for dose selection; use of dietary administration without documentation of stability of drug in diet or plasma exposure; inadequate dosing period, incomplete individual line listings.

Toxicokinetic bridging studies were not conducted; therefore, estimates of plasma exposure are not available for the mouse, rat, or rabbit studies. The inability to estimate plasma exposure is deemed a serious deficiency relevant to all of the studies conducted with dietary administration of the drug. These limitations are particularly germane to the carcinogenicity studies, given the group housing and lack of drug stability data.

Although these are significant deficiencies, Drs. Fisher and Freed believe that they can be addressed post-approval, in light of the seriousness of the clinical indication and the extensive postmarketing clinical experience (outside of the U.S.). Dr. Brown agrees with their assessments and plans.

Dr. Freed recommends that the applicant be required to conduct a full battery of reproductive and developmental toxicity studies (as described in International Conference on Harmonization [ICH] guidance) and carcinogenicity studies in two species, all under GLP. In addition, the applicant should be required to provide steady-state toxicokinetic data in the animal species used for these studies, at relevant doses. These will be addressed as postmarketing requirements (PMRs, see approval letter).

Carcinogenicity

In vitro genetic toxicology and carcinogenicity studies were negative.

In vivo carcinogenicity studies revealed a non-statistically significant increase in hepatocellular adenomas in male mice (there were no hepatocellular carcinomas), as well as a dose-related increase in thyroid follicular cell adenomas in male rats, statistically significant at the high dose. There were no carcinomas or other tumors.

These studies were deemed inadequate for a number of reasons, including but not limited to: 1) limited statistical power: several animals died secondary to fighting, and treatment duration was

reduced; 2) unknown reliability of dietary drug dosing, with food and drug consumption computed by *cage* and no assessment of toxicokinetics; 3) lack of documentation of the numbers and types of organs examined microscopically, with the assumption that any organ not reported was tumor-free; and 4) lack of adherence to GLP.

The inadequacies of the studies notwithstanding, the Executive Carcinogenicity Assessment Committee concluded there were no significant drug-related neoplasms in mice and that the increase the thyroid follicular cell adenomas in high-dose rats was drug-related.

Dr Fisher and Freed conclude that, considering the serious nature of the disease, the inadequacies of these carcinogenicity studies should not delay approval of clobazam, but that supplemental studies should be required as PMRs. Such studies should also include toxicokinetic data, which were lacking in the original studies.

Reproductive and Developmental Toxicity

Although the developmental studies, conducted in the 1970's, lack the rigor of today's GLP studies and suffer from a number of limitations (dosing periods did not involve the entire period of organogenesis, inadequate doses, lack of justification for the selected doses, inadequate evaluation of some endpoints), an increased incidence of cleft deformities was observed in high-dose mice. Cleft deformities have been reported in humans for benzodiazepines, but Dr. Fisher specifically notes that more recent publications have failed to confirm this. Thus, although these studies were deemed deficient, the team opined that there are sufficient data to support approval, but that additional data should be obtained from studies performed as PMRs.

Site Inspections:

DSI staff has inspected 3 domestic sites and 1 foreign site. They found regulatory violations for 2 investigators; however, "…the findings are not likely to critically impact primary efficacy and safety analyses…". "Overall, the data submitted from these sites are considered acceptable in support of the pending application."

Pharmacokinetics:

Clobazam exhibits dose-proportional pharmacokinetics over a dose range of 10 to 80 mg. Absorption is moderate to rapid, with T_{max} ranging from 0.5 to 4 hours after administration of single or multiple doses. Crushing pills has no effect on absorption. Administration with a high-fat meal has no clinically significant effects on clobazam's pharmacokinetics, and the drug can be taken without regard to meals.

Clobazam is widely distributed, with an apparent volume of distribution of [redacted]. Clobazam and its active metabolite, N-desmethylclobazam, are moderately protein-bound.

Clobazam is cleared mainly by metabolism with subsequent renal elimination of metabolites. In a mass balance study, 82% of the administered dose was recovered in urine (2% unchanged) and 11% in feces. Clobazam's major metabolic pathway involves N-demethylation to form N-desmethylclobazam, the only pharmacologically active metabolite. N-demethylation is mediated primarily by CYP3A4, and to a lesser extent by CYP2C19 and CYP2B6. N-desmethylclobazam, plus the sum of its metabolites, comprises ~94% of the total drug-related components in urine.

N-desmethylclobazam is itself extensively metabolized, mainly by CYP2C19. Plasma levels of N-desmethylclobazam were higher in CYP2C19 poor metabolizers than in wild type subjects, and this language will be included in labeling.

In healthy adults and patients, clobazam oral clearance (CL/F) ranges from [redacted] and its mean terminal half-life ($T_{1/2}$) is 36 to 42 hours. The mean steady-state $T_{1/2}$ of N-desmethylclobazam is 71 to 82 hours.

Special Populations

For a number of special conditions where clobazam's elimination may be slowed, the clinical pharmacology staff has recommended dosing adjustments – generally a lower starting dose and less rapid titration – without limiting the upper dose. This strategy is meant to provide adequate time for evaluation of clinical status at each dosage step, given the longer period required to reach steady state at each step. These recommendations are:

- Because population pharmacokinetics reveals a lower clearance in the elderly, dosage adjustments are recommended. No adjustments are recommended based on race, ethnicity, or sex.
- No dosage adjustment is recommended for patients with mild or moderate renal impairment, as C_{max} and AUC are not significantly increased, as determined in a dedicated study in patients with renal impairment. The applicant provided a single case study suggesting that dosage adjustment is unnecessary in patients with end-stage renal disease (ESRD) on dialysis; however, this information was not deemed adequate by the review team, and dosage adjustments may be needed in such patients. There is no information available on whether clobazam is dialyzable. The lack of information for patients with severe renal disease and ESRD will be noted in labeling.
- Based on a published report in 9 patients, mild and moderate hepatic impairment have little effect on clobazam's pharmacokinetics. Because of the inherent limitations of the data, however, the review team suggested only reduction of the initial dose, with titration as tolerated. The data for severe hepatic impairment were deemed inadequate, thus no dosing recommendations can be provided in labeling.
- Compared to intermediate and extensive metabolizers, CYP2C19 poor metabolizers experience 3-5 fold higher N-desmethylclobazam concentrations (C_{max} and AUC), with no change in exposure to the parent drug. The label is worded to make dosing recommendations for patients "…known to be CYP2C19 poor metabolizers," so as not to imply mandatory genetic testing.

Drug Interactions

Clobazam is an inhibitor of CYP2D6, *in vivo*; drugs metabolized by CYP2D6 may require dose adjustment when used with clobazam. Clobazam is also a mild inducer of CYP3A4. The effect is relatively small, such that dose adjustment is unnecessary for most drugs; however, CYP3A4 induction may have clinically important effects on metabolism of hormonal contraceptives, and this concern is addressed in labeling. Because N-desmethylclobazam, an active metabolite, is primarily metabolized by CYP2C19, dosage adjustment is being recommended when strong and moderate CYP2C19 inhibitors are used concomitantly with clobazam. The label is worded to make such recommendations for patients "…known to be poor metabolizers," so as not to imply mandatory genetic testing.

Neither clobazam nor N-desmethylclobazam inhibits P-glycoprotein (P-gp), but they are P-gp substrates.

A variety of anticonvulsants were evaluated for their potential effects on the pharmacokinetics of clobazam and N-desmethylclobazam. CYP3A4 inducers (phenobarbital, phenytoin, and carbamazepine), CYP2C9 inducers (valproic acid, phenobarbital, phenytoin, and carbamazepine), and CYP2C9 inhibitors (felbamate and oxcarbazepine) had no important effects on metabolism of clobazam.

Thorough QT Study:

The effect of clobazam on QTc interval was evaluated in a randomized, evaluator-blinded, placebo-, and active-controlled (moxifloxacin 400 mg) parallel thorough QT study. Clobazam was administered twice daily at 40 and 160 mg. The study demonstrated adequate assay sensitivity, based on the response to moxifloxacin. The upper bound of the 1-sided 95% confidence interval (CI) for the largest placebo adjusted, baseline-corrected QTc (Fridericia method) was <10 ms, which is the threshold for regulatory concern per ICH E14 Guideline. The exposures produced in the study following the 160-mg dose cover anticipated high-exposure scenarios (use of ketoconazole and alcohol).

Evidence of Effectiveness:

The applicant submitted two randomized controlled (phase 3) trials to establish clobazam's evidence of effectiveness for the "adjunctive treatment of seizures associated with LGS in patients 2 years of age or older." Study OV-1012 (referred to as study 1012 in this memorandum) was identified as the principal study, and study OV-1002 (referred to as study 1002) as supportive, although this distinction is not meaningful. Both are adequate and well controlled studies that support the effectiveness of clobazam in LGS. Results of study 1012 were recently published.[1]

Study 1012

Study 1012 was a multinational, randomized, double-blind, 4-arm study, to compare clobazam at low, medium, and high doses to placebo. Target doses for the low, medium and high groups were approximately 0.25, 0.5, and 1.0 mg/kg/d, respectively. Patients were stratified according to baseline weight (≤ 30 kg; > 30 kg), and target doses computed as per Table 1. Doses in the table represent total daily doses, which were administered as divided doses, given twice daily (except the 5 mg daily dose was given daily):

Table 1: Study 1012 – Dosing Paradigm

	Clobazam Total Daily Dose	
Dose Group	**≤ 30 kg body weight**	**>30 kg body weight**
Low (~ 0.25 mg/kg/d)	5 mg	10 mg
Medium (~ 0.5 mg/kg/d)	10 mg	20 mg
High (~ 1 mg/kg/d)	20 mg	40 mg

The study consisted of a 4-week baseline period, a 3-week titration period, and a 12-week maintenance period, followed by a 2- or 3-week taper period or entry into a long-term, open-label extension study.

Key inclusion criteria included:

- age 2 to 60;
- weight ≥ 12.5 kg;
- a diagnosis of LGS based on > 1 type of generalized seizure, including drop seizures for ≥ 6 months, a history of meeting EEG criteria for LGS;
- ≥ 2 drop seizures per week during the 4-week baseline period;
- receipt of ≥ 1 antiepileptic drug (AED), on a stable AED regimen for ≥ 30 days.

During the 3-week titration period, total daily doses of either 5 or 10 mg clobazam (or matching placebo) were initiated, with doses increased weekly until the target dose was reached. A single back-titration of 5 mg was allowed for patients who were unable to tolerate the drug because of side effects.

The subject's caregiver recorded the daily number of drop seizures, clusters, and cluster sizes on diary cards. The exact number of drop seizures or a numeric range (10-20 drop seizures or >20 drop seizures) could be recorded. Imputation was carried out as follows:

- for the range of drop seizures of 10-20, a value of 10 was imputed;
- for the observation of drop seizures >20, a value of 20 was imputed;
- for "too many to count," 20 was imputed;
- for "unknown," a value of 1 was imputed for a single drop seizures; a value of 10 was imputed for a cluster of drop seizures;
- "not done" was not imputed, i.e., it was considered missing.

Values for drop seizure rates were calculated as seizures per week, as follows:

[(number of seizures recorded)/(number of days of observation)] X 7

The primary endpoint was the percent reduction in the weekly average frequency of drop seizures from the 4-week baseline period to the 12-week maintenance period, evaluated by an analysis of covariance (ANCOVA) using the modified intent to treat (mITT) analysis set with percent reduction in drop seizures as the dependent variable and treatment, center, and baseline drop seizure rate as the independent variables. The mITT population was defined as all randomized subjects who had baseline data, had received ≥1 dose of study drug, and had ≥1 daily seizure measurement during the maintenance period.

The primary analysis compared each clobazam arm to placebo in pairwise fashion, using a step-down procedure, starting with the highest dose and proceeding to the lowest dose.

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[1] Ng YT, Conry JA, Drummond R, et al. Randomized, phase III study results of clobazam in Lennox-Gastaut syndrome. Neurology 2011;77:1473-81.

Alpha was set at 0.01, with the goal of providing robust statistical evidence, sufficient to support approval on the basis of this single study with supportive information, consistent with FDA guidance.[2]

Multiple sensitivity analyses were prospectively planned for the 1° endpoint, and these are outlined by the review team.

There was a plethora of secondary endpoints, including:

- percent reduction in seizures from baseline to the first, middle, and last 4 weeks of maintenance;
- a responder analyses on drop seizure rates, with a separate analysis by initial, middle, and end of maintenance period;
- percent change in non-drop seizures;
- percent change in total seizures;
- assessment of tolerance. A patient was considered a responder if he or she had at least a 50% reduction in drop attacks during the first 4 weeks of maintenance compared to baseline. The number and percentage of responders who returned to their baseline seizure rate during the last 4 weeks of maintenance, or those who discontinued for lack of efficacy were compared between groups. An analysis was also done using a definition of responder based on the first 8 weeks of maintenance.
- use of rescue medicine;
- physician and parent/caregiver global evaluation.

All 2° endpoints were to be evaluated at an alpha of 0.05. There was no plan to control alpha for the group of secondary endpoints, so that positive results on these endpoints would be difficult to interpret.

Results:

A total of 238 subjects were randomized at 53 sites, predominantly in the U.S (35 sites; 69% of subjects) and India (13 sites; 24% of subjects), with 5 sites in Europe and Australia (7% of subjects). There were 59, 58, 62, and 59 patients randomized to the placebo, low-, medium-, and high-dose groups, respectively.

Overall, 74% of subjects completed the study. Discontinuations were approximately 30% in the high-dose, medium-dose, and placebo groups, but lower in the low-dose group where there were about half as many (14%). The most common reasons for discontinuation were lack of efficacy in the placebo group and adverse events in the clobazam groups. The percentage of subjects discontinuing in association with adverse events increased with increasing clobazam dose: 3% placebo, 7% low-dose, 13% medium-dose, and 20% high-dose.

Demographic variables were generally similar between treatment groups. Mean age (overall) was 12 years (range 2 to 54), and mean weight was 35 kg. The demographic makeup was approximately 60% male, 60% Caucasian, 25% Asian, 10% African American, and 12% Hispanic.

[2] Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, May, 1998

The baseline drop seizure rate was, however, 40% lower in the medium-dose group than that in the other groups. This is discussed below.

Of the 238 subjects randomized, 217 met criteria for the mITT analysis.

Dr. Siddiqui's analysis of the primary endpoint, percent reduction of drop attacks, is summarized in Table 2. His results differ only slightly from those of the applicant. For clobazam, the reviewers noted an apparent dose-response in seizure rate reduction. Differences in seizure rates in the high- and medium-dose groups were statistically significantly superior to placebo at

Table 2: Study 1012 – Percent Reduction in Average Weekly Rate of Drop Seizures (Baseline to Maintenance Period) – mITT Population

		Clobazam Dose Group		
	Placebo	Low	Medium	High
	N = 57	N = 53	N = 58	N = 49
Baseline drop seizures per week				
Mean (SD)	97.8 (171)	99.6 (206)	60.5 (123)	105.2 (163)
Median	35.5	29.2	22.5	46.4
Range	2, 920	2, 1077	2, 798	2, 856
% reduction during maintenance period				
Mean (SD)	12.5 (72.7)	41.6 (46.8)	47.8 (62.0)	69.5 (39.7)
Median	23.2	46.7	57.9	86.5
Range	-374, 100	-119, 100	-262, 100	-39, 100
p-value: comparison to placebo		0.012	0.0015	< 0.0001

a p-value <0.01; the low-dose group was statistically significantly better than placebo at a p-value of 0.012. Although all 3 doses are effective, the author notes, however, that there is little difference in percent seizure reduction between the low and medium clobazam groups, and a large difference between the high dose and the medium doses.

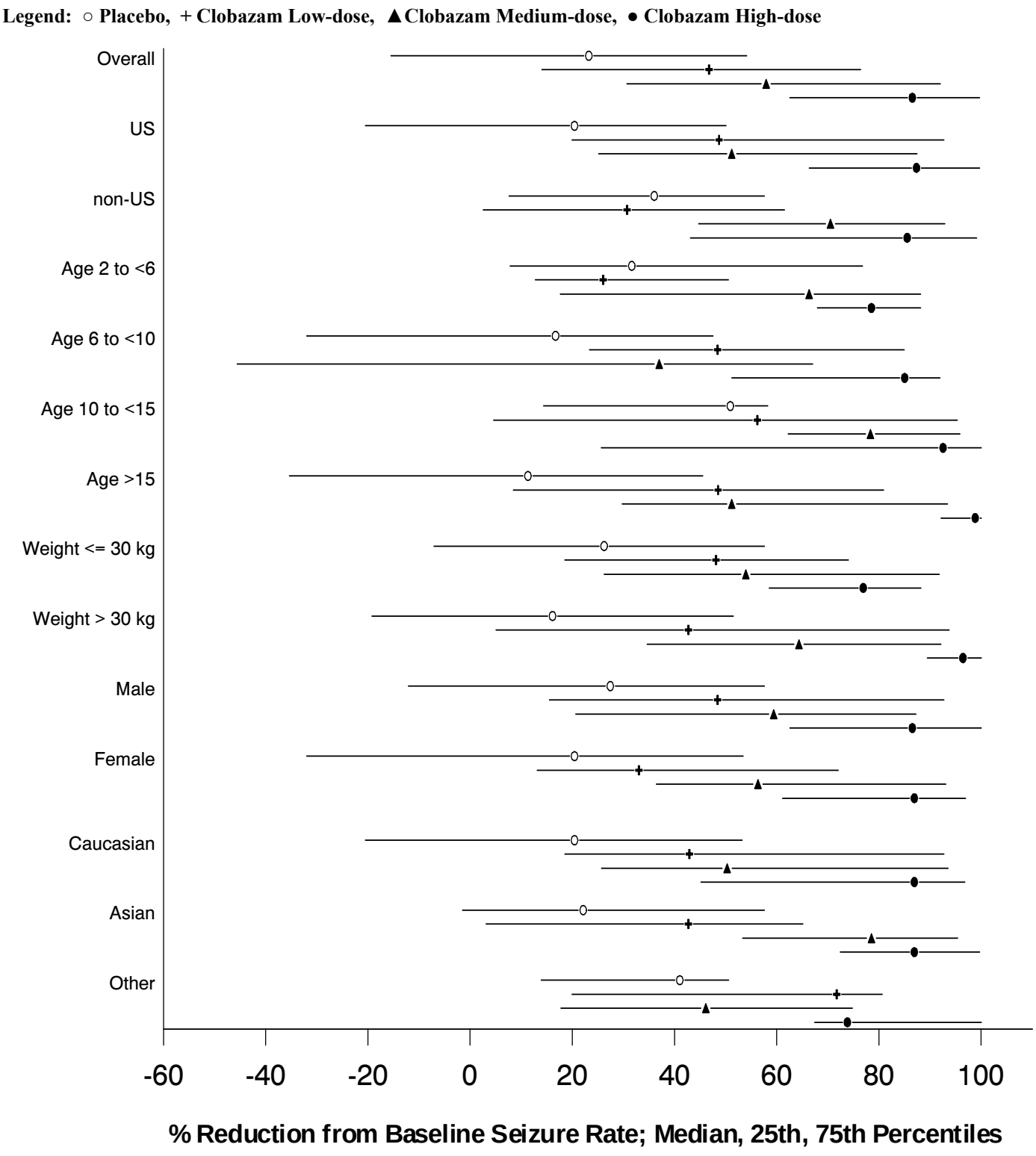
The p-values were similar when analyzed using a non-parametric Wilcoxon rank-sum test. Results in the medium- and high-dose groups were robust to a number of planned sensitivity analyses.

Subgroups:

Results were consistent across subgroups of geographic region (U.S., non-U.S.), weight, sex, and race (Figure 1). The analysis shown by applicant and the statistical reviewer show an apparent lack of treatment effect in patients aged 12 to 17. Drs. Siddiqui and Hershkowitz opined that this was most likely a function of the limited sample in the stratum (the 12 to 17 age stratum included only ~16% of the subjects). The author divided subjects roughly into quartiles by age, and the treatment effect seems consistent across age groups. The author also analyzed results by baseline frequency of seizures (in quartiles), and results were consistent

(data not shown). Results were also consistent for age of onset of LGS, history of status epilepticus, and history of infantile spasms (data not shown).

Figure 1: Study 1012: Subgroup Analysis on Primary Efficacy Endpoint



Missing Data:

To evaluate the impact of missing data, ANCOVA analyses were conducted to compare the baseline seizure rate to the rates during the initial, middle, and final 4-week intervals of the maintenance period, i.e., Weeks 4 to 7, 8 to 11, and 12 to 15, respectively. The weekly seizure rates were calculated over the number of days with non-missing seizure data (Table 3).

The high-dose clobazam group was statistically significantly superior to placebo within all 3 intervals (Table 3). The medium-dose clobazam group was statistically significantly superior to placebo for the initial and final intervals in the maintenance period (the p-value was 0.22 for the middle interval). The low-dose clobazam group was statistically significantly superior to placebo for the initial interval in the maintenance period; the p-value was approximately 0.1 for the other intervals. These findings suggest that missing data had no major impact on the primary endpoint in study 1012.

Table 3: Study 1012 – Percent Reduction in Average Weekly Rate of Drop Seizures (Baseline Compared to First, Middle, and Last 4 Weeks of Maintenance Period) – mITT Population

		Clobazam Dose Group		
	Placebo	Low	Medium	High
Interval of Maintenance Period				
First 4 weeks (Weeks 4-7)	N = 57	N = 53	N = 58	N = 49
Baseline median seizure rate	35.5	29.2	22.5	46.4
Maintenance median seizure rate	25.6	14.2	3.5	4.6
Median percent reduction in seizure rate	30.7	44.4	72.7	92.1
p-value: comparison to placebo		0.002	<0.001	<0.001
Middle 4 weeks (Weeks 8-11)	N = 47	N = 52	N = 53	N = 44
Baseline median seizure rate	25.8	28.9	23.5	45.4
Maintenance median seizure rate	15.5	15.9	9.9	4.5
Median percent reduction in seizure rate	38.8	48.9	57.1	88.1
p-value: comparison to placebo		0.104	0.22	0.002
Last 4 weeks (Weeks 12-15)	N = 44	N = 51	N = 46	N = 42
Baseline median seizure rate	31.9	29.2	22.6	42.6
Maintenance median seizure rate	25.3	17.2	7.3	4.1
Median percent reduction in seizure rate	35.6	46.8	69.2	89
p-value: comparison to placebo		0.146	0.016	0.002

For non-drop seizures, clobazam had no statistically significant treatment effect at any dose, although there were dose-related trends. The applicant showed a statistically significant treatment effect for the high-dose group, but only using a *post hoc* nonparametric analysis. When all seizures (drop and non-drop) were combined, the results were similar to those for drop seizures alone.

Tolerance:

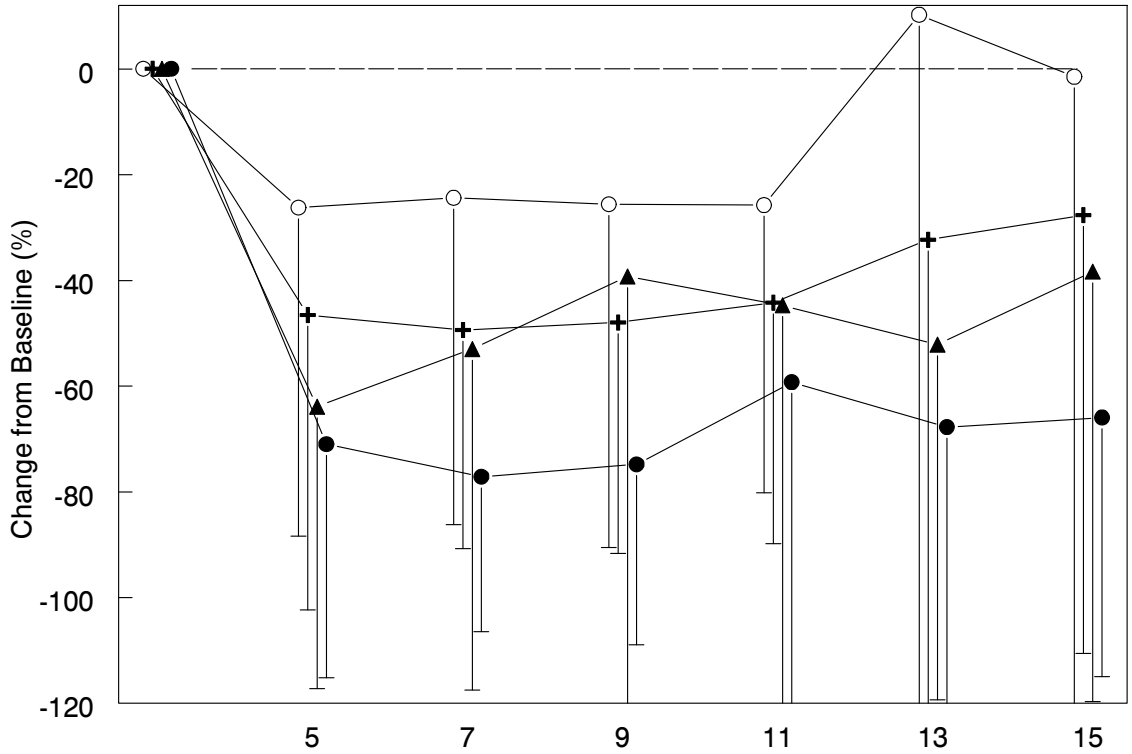
Because tolerance is known to develop with the benzodiazepine class of drugs, examination of tolerance was a particularly important secondary endpoint. As noted under Regulatory History, the study was lengthened from the 8 weeks initially planned to 12 weeks, to better evaluate the development of tolerance. Tolerance was assessed by comparing responses during the first 4 weeks of the maintenance period to those during the last 4 weeks of the maintenance period. For each treatment group, the applicant identified subjects who achieved a ≥ 50% reduction in the rate of drop seizures from baseline to the first 4 weeks of the maintenance period, and determined the fraction of these subjects who experienced a return to baseline seizure frequency during the final 4 weeks of the maintenance period (or who discontinued for lack of efficacy). According to this analysis, 5.3% to 9.5% of subjects in the clobazam treatment groups fulfilled this definition of tolerance as compared to 5.6% patients in the placebo group. Dr. Hershkowitz points out some concerns regarding this analysis: 1) the analysis was based on a ≥50% response during the first 4 weeks of maintenance, i.e., subjects who experience a fairly robust treatment effect; and 2) the return to baseline seizure frequency is an anti-conservative criterion for loss of effect. In essence, Dr. Hershkowitz's concern is that lesser losses could be important as well.

He notes that the analyses the applicant performed to evaluate the effect of missing data partially addresses tolerance issue. There were no important differences in responses between the initial and final 4 weeks of the maintenance period (Table 3). Dr. Hershkowitz points out, however, that these response rates are affected by dropouts, which may not be random events. He also noted, however, that an analysis of an open-label extension study (OV-1004) for periods greater than 1 year suggested long-term persistence of therapeutic effect. This open-label study has limitations, but it generally supports a persistent treatment effect.

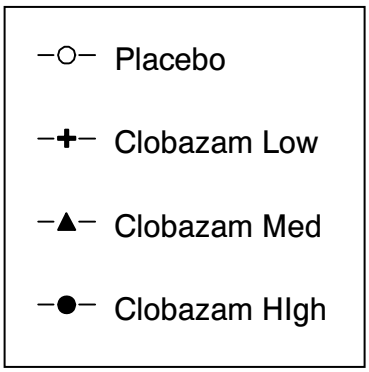
Figure 2 shows the author's analysis of change in seizure frequency from baseline by week. Weeks 1 through 3 constitute the baseline period; Weeks 5, 7, 9, 11, 13, and 15 constitute the maintenance period. There appears to be a decrease in seizure rate in the placebo group at Week 5, although the rate returns to baseline at Week 13 (despite considerable loss of subjects, many for lack of efficacy). For all 3 clobazam groups, there appears to be slight loss in efficacy from Weeks 5 to 15, based on gently uprising slopes in the point estimates. It is important to recognize, however, that variability is great (the plot shows standard deviations in the negative direction), and the data are consistent with increasing, decreasing, or no change in efficacy through time.

The also author performed a linear regression (least squares) for each subject, analyzing percent reduction in seizures as a function of time for the 12-week maintenance period. The slope of this relationship is percent reduction in the seizure rate per week: a positive value denotes improving seizure control; a negative value denotes worsening. For the low-, medium-, and high-dose clobazam groups, the mean slopes were -2.0, -2.3, and -0.9 percent reduction in seizure rate per week. Although negative slopes are consistent with loss of efficacy over time, again, the confidence intervals are wide, and include positive slopes. Thus, the analysis is inconclusive.

Figure 2: Study 1012 – Percent Reduction in Drop Seizures by Week, Mean Minus SD



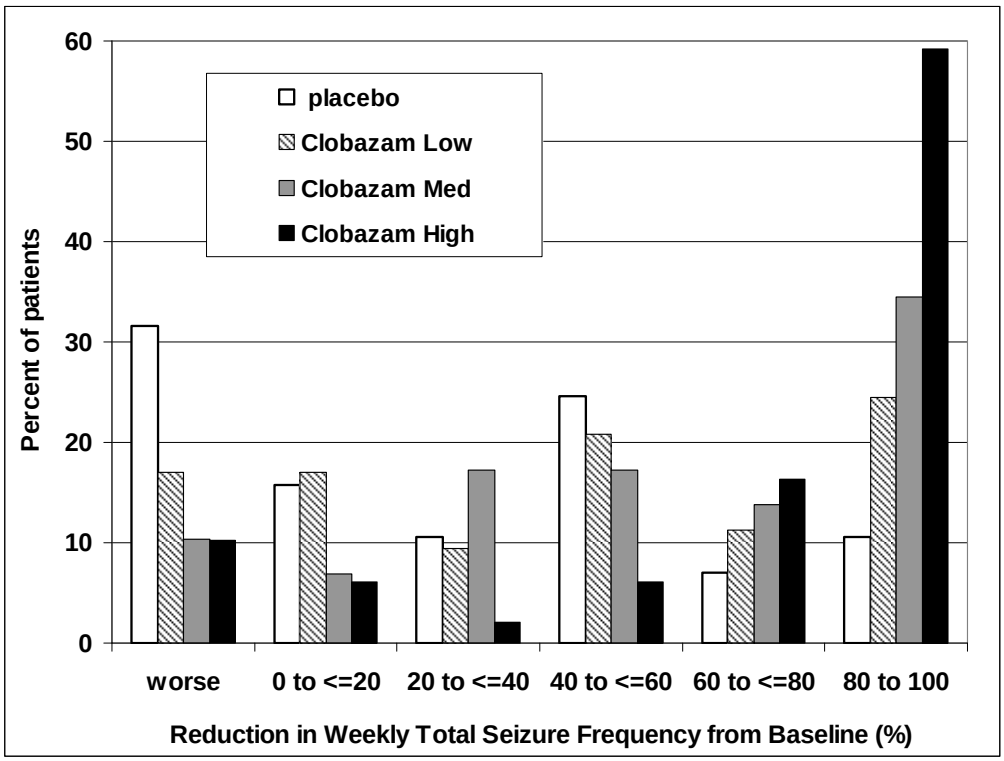
N:							
placebo	57	50	47	46	44	42	56
clobazam low	53	53	52	52	51	50	52
clobazam med	58	55	52	50	46	45	58
clobazam high	49	44	42	42	41	41	49



Display of Individual Responses:

There is much interest in displaying individual responses in labeling, in addition to the mean response. The applicant provided a cumulative distribution plot to show individual responses. Although such plots can be used to depict individual responses, the Division has concluded that interpretation of such displays is challenging, so that in recent NDAs we have been using histograms to show the spectrum of responses across treatment groups. The author's histogram (from the dataset ads_1012.xpt) is shown in Figure 3.

Figure 3: Study 1012 – Histogram Showing Responses in Drop Seizures by Category



Study 1002

Study 1002 was a phase 2, multicenter, randomized, double-blind, parallel-group study comparing the high and low doses of clobazam used also in Study 1012 (there was no placebo arm). It was conducted at 13 sites in the U.S. The baseline and titration periods were identical to those in Study 1012, but the maintenance period was only 4 weeks in duration (the maintenance period was 12 weeks in Study 1012). The primary endpoint (percent change in drop seizures) and its analysis were similar to those in Study 1012, except the low dose was compared to the high dose and analysis used non-parametric testing.

A total of 68 patients were randomized. Demographics were generally similar between groups. Baseline seizure activity was substantially higher in the high-dose group.

Results of the primary endpoint analysis are presented in the table below (transcribed form the statistical review). The high dose group exhibited a statically significant greater control then the

low dose group. Secondary endpoints were similarly affected as they were in study OV-1012. In particular, there was a significant reduction in non-drop seizures when comparing the high to low dose. An analysis by the Dr. Siddiqui, the statistical reviewer, confirmed the Sponsor's analysis.

Table 4: Study 1002 – Percent Reduction in Average Weekly Rate of Drop Seizures (Baseline to Maintenance Period) – mITT Population

	Clobazam Dose Group	
	Low N = 29	High N = 32
Baseline drop seizures per week		
Mean (SD)	142.0 (190.2)	209.1 (229.2)
Median	66	97
Range	5, 661	8, 924
% Reduction during maintenance period		
Mean (SD)	10.1 (122.3)	85.2 (17.1)
Median	29	93
Range	-531, 100	48, 100
p-value (low vs. high)		< 0.0001

Drs. Sheridan and Hershkowitz note that although this study was presented as "supportive," that is a "distinction without a difference," and Study 1002 is a well controlled study that provides strong evidence of efficacy. Its principal limitation was its inability to examine tolerance because of its short duration.

Safety:

The safety data have been extremely well considered and summarized by Drs. Boehm, Yasuda, Hershkowitz, and Katz. Special issues have been addressed by the QT Interdisciplinary Review Team and Controlled Substance Staff.

The applicant provided safety data from 56 clinical trials that included 2,236 exposed subjects. Eleven (11) of these trials were conducted by Lundbeck: 3 were phase 2/3 LGS trials (the 2 randomized-controlled efficacy trials [1012 and 1002] and the open label extension of 1012), and 8 were phase 1 studies. In total, the applicant's studies included 633 subjects. The applicant supplemented these data with safety data from 45 trials conducted by previous sponsors, referred to as "legacy trials," conducted in the 1970s, 80s, and 90s. These were obtained from non-US clinical development programs, and in many cases lack source data. The legacy data did include 1 trial in children with epilepsy (study 301), but the others were in patients with psychiatric diseases (including anxiety and neuroses).

Considering only the clinical trials conducted by Lundbeck, the exposure does not meet the ICH guideline recommendations, but of course LGS is an orphan indication, and adherence to ICH Guidelines in terms of patient numbers is not expected. Of the 633 subjects exposed to clobazam in the LGS development program, 253 were exposed to clobazam for at least 6 months, 197 for at least 12 months, and 100 for at least 24 months. Inclusion of the subjects in

the legacy trials increases the number of exposed patients to 2,236, but, as pointed out by Dr. Boehm, many of these trials lack clobazam dose, start dates, stop dates, and source data.

In addition to the legacy trials, there is also postmarketing experience with clobazam from some 40 years of marketing outside the U.S., and the applicant summarized spontaneous postmarketing adverse event reports and published reports of adverse events that mentioned clobazam.

Key Safety Issues:

Somnolence and Sedation: In Study 1012 (the only randomized placebo-controlled study in LGS), somnolence was reported in 25% of clobazam-treated subjects at the medium and high doses, vs. 12% in placebo. Sedation was reported in 9% of clobazam-treated subjects at the high dose, vs. 3% in placebo. Although the applicant argues that sedation and somnolence are distinct and separable entities, Dr. Boehm does not view this distinction to be feasible, given the way that adverse events were collected. Thus, the review team prefers to provide an overall accounting of a combined term of "somnolence or sedation." The important information to convey in labeling is that clobazam causes these events (at a rate approximately twice placebo), and that these side effects are dose-related.

Withdrawal: Withdrawal is a major concern for two reasons. First, benzodiazepine withdrawal syndrome is a well-described, clinically important phenomenon. Second, as with all AEDs, rapid withdrawal can precipitate seizures, or even status epilepticus.

As noted by the safety review team, withdrawal-related adverse events were evaluated in phase 1 trials, where clobazam (including high doses) was abruptly stopped without tapering. Withdrawal was also assessed in phase 2 and 3 LGS trials where subjects who discontinued clobazam received tapering doses. In phase 1 trials, one-third of subjects experienced withdrawal-related adverse events, the majority of which were reported within the first week. Dr. Boehm notes that the risk appears to increase with clobazam dose; however, an objective assessment of withdrawal using the Clinical Institute Withdrawal Assessment-Benzodiazepines (CIWA-B) questionnaire did not find a clear relationship between withdrawal risk and dose.

The most commonly reported withdrawal adverse events were headache, insomnia, anxiety, tremor, palpitations, hyperhidrosis, irritability, decreased appetite, diarrhea, and visual changes. In the Phase 2 and 3 LGS trials where clobazam was to be tapered rather than abruptly discontinued, no withdrawal-related adverse events were reported in the 93 subjects who discontinued the drug. Thus, the labeling will make the point that discontinuation of clobazam can cause withdrawal, particularly when abrupt, and that the risk increases with increasing dose, though this is less well substantiated.

Dependence: The Controlled Substances Staff recommends listing clobazam in Schedule IV of the Controlled Substances Act.

Suicidality: The clobazam NDA included limited data to assess suicidality risk. The applicant restricted their analyses to randomized, parallel-arm, placebo-controlled trials with ≥20 subjects per treatment arm, at least 5 years of age, and with study length at least 7 days. Considering only trials that met these criteria, there were no suicidality adverse events in the clobazam LGS development program. In the legacy psychiatry trials, 1 suicide attempt and 2 adverse events of suicidal ideation were reported in clobazam-treated subjects.

Overall Issues:

Evidence of Effectiveness: I agree with the review team on the evidence of effectiveness. The level of evidence here is compelling. The results are statistically persuasive, robust to sensitivity analyses, and consistent across the principal subgroups of interest.

Although Study 1002 is characterized as a phase 2 "supportive" study, the results are statistically and clinically compelling, and the absence of a placebo group is not germane to its evidence of effectiveness. The "Achilles heel" of Study 1002 is its short duration – inadequate to assess the possibility of tolerance. Study 1012 had a 12-week maintenance phase, which was deemed adequate in length to evaluate tolerance. The results tend to support durability of clobazam's effect, but also show very clearly that the variability in response precludes a true assessment of durability/tolerance. At best, one can only get a sense of tolerance, or lack of tolerance, from the point estimates of the seizure rates at various points in time.

Adequacy of Dose Exploration/Dose Recommendations for Labeling: The applicant studied clobazam's efficacy at a range of doses: 0.25, 0.5, and 1.0 mg/kg/d. Seizures are important events, and the goal of therapy is to gain seizure control, generally by pushing doses of AEDs to high levels, and reducing doses as necessary for important side effects. Thus, unlike therapies for symptomatic conditions, identification of a minimally effective dose for AEDs seems irrelevant. In terms of exploration at the high end of the dosing spectrum, adverse events in the nervous system "System Organ Class" were reported in 58% of subjects at the highest dose studied, including somnolence in 25% of subjects. Thus, exploration at the high end of the dose range appears to have been adequate in this development program. The label will stress that each dose of clobazam has been shown to be effective, but effectiveness increases with increasing dose.

Advisory Committee: This application was not referred to the Peripheral and Central Nervous System Drugs Advisory Committee. Although clobazam is a new molecular entity, it belongs to well characterized drug class (benzodiazepines), and the disease for which the drug is indicated (epilepsy) is well-studied, with numerous approved AEDs. Moreover, the primary efficacy endpoint (seizures) is well understood, and the treatment effect was substantial. Absent other critical review issues, the Division decided, and the Office concurred, that not taking the application to an advisory committee was reasonable and justified.

Pregnancy Category C: Other benzodiazepines carry a designation of pregnancy Category D or X; these determinations were based on the Agency's interpretation, many years ago, of reports of birth defects in humans. More recent data and analyses do not appear to support these earlier concerns. In light of this thinking, the review team, after much deliberation, decided to designate clobazam as Category C. (b) (4)

Carcinogenicity and Reproductive Toxicity Studies: As noted above, many of the carcinogenicity and reproductive toxicity studies are inadequate by today's standards. But all members of the review team have agreed that these inadequacies can be addressed in the postmarketing period as PMRs. This conclusion was based on several considerations: 1) the seriousness of the disease; 2) the limited treatment options approved for this disorder (and their toxicities); 3) the extensive postmarketing experience for clobazam; and 4) some data are, in

fact, extant. The approval letter will contain a number of post-marketing requirements related to this area.

Conclusions:

For the reasons stated above, I am today approving the NDA for clobazam for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients 2 years of age or older. Postmarketing requirements and commitments are delineated in the approval letter, and approved labeling is attached.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELLIS F UNGER
10/21/2011